



MOX–Report No. 18/2009

**A mathematical model for water uptake, degradation,
erosion, and drug release from degradable polydisperse
polymeric networks**

JOÃO SILVA SOARES, PAOLO ZUNINO

MOX, Dipartimento di Matematica “F. Brioschi”
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

mox@mate.polimi.it

<http://mox.polimi.it>

A mathematical model for water uptake, degradation, erosion, and drug release from degradable polydisperse polymeric networks¹

João Silva Soares, Paolo Zunino

July 7, 2009

Modelling and Scientific Computing (MOX)

Dipartimento di Matematica “F. Brioschi”

Politecnico di Milano

Piazza Leonardo da Vinci 32, 20133 Milano, Italy

joao.soares@polimi.it

paolo.zunino@polimi.it

Keywords Hydrolysis, scission, polylactic acid, reaction-diffusion, bulk erosion, surface erosion, drug delivery

Abstract

We introduce a general class of mixture models to study water uptake, degradation, erosion, and drug release from degradable polydisperse polymeric matrices. The mathematical model is based on a finite number of constituents describing the polydisperse polymeric system, i.e. each representing collection of chains whose size belongs to a finite interval of degree of polymerization. In order to model water uptake and drug release, two additional constituents (water and drug) constitute the mixture.

Constituents diffuse individually accordingly to Fick’s first law and balances of mass of constituents yield partial differential equations that govern the reaction-diffusion

¹ This work has been supported by the Grant “Nanobiotechnology - Models and methods for degradable materials” by the Italian Institute of Technology and by the European Research Council Advanced Grant “Mathcard, Mathematical Modelling and Simulation of the Cardiovascular System”, Project ERC 2008 AdG 227058. JSS thanks CEMAT for their support.

system. Hydrolysis, a chemical reaction that breaks down larger chains into smaller ones, is accounted with reactions terms quantifying sources and sinks of polymeric chains and a sink of water. Hydrolysis couples the system of equations and nonlinearities appear through constitutive specification of the diffusivities of constituents on the current network, reaction rates, and boundary conditions.

The mathematical model is independent of the number of constituents describing the polydisperse polymeric system and hydrolysis kinetics describe with accuracy the overall decrease in molecular weight distribution and satisfies a monomer conservation principle. A shift between two different types of solutions of the system of partial differential equations, each identified to surface or bulk erosion, is obtained with the variation of a single non-dimensional number, the Thiele modulus, which measures the relative importance of the mechanisms of reaction and diffusion. Results of drug release confirm that drug release from bulk eroding matrices is diffusion-controlled, whereas for surface eroding polymers, drug release is enhanced in an erosion-controlled process.

1 Introduction

Polymer-based systems have had an enormous impact on drug delivery therapies [1]. The techniques employed today differ in concept but all of them share one particular feature, the mechanism of diffusion of certain species, the drug, through a matrix, usually polymeric in nature. In one approach, the drug is physically entrapped in a solid polymer capsule that can be injected or implanted in the body. Early forms of these systems involved non-degradable polymers in membrane-controlled diffusion such as silicone rubber, which could release low molecular weight drug for extremely long times [2]. Alternatively, drugs were also physically embedded in polymers at concentrations high enough to create a series of interconnecting pores through which the drug could afterward slowly diffuse from a matrix system [3]. Subsequently, biodegradable polymers were utilized, where the combination of diffusion through the pores as well as polymeric matrix degradation and erosion allows controllable release rates [4].

The process of degradation and erosion of polymers, i.e. the loss of mechanical integrity due to extensive backbone chain scission, has received particular attention recently as the availability and utilization of synthetic biodegradable polymers has increased dramatically over the last 50 years [5]. Degradable materials have found a wide variety of applications in the medical field ranging from biodegradable sutures [6], pins and screws for orthopedic surgery [7], local drug delivery [1], tissue engineering scaffolds [8], and biodegradable endovascular and urethral stents [9,10]. When used for load-bearing applications, the contribution of the polymer is required for a limited period of time, the healing time, and the polymer can be engineered to degrade at a rate that will transfer the load to the healing tissue, which require the understanding of the load bearing capabilities of the device as well as their evolution due to degradation over time [11]. On the other hand, for drug delivery implants, attention is shifted to delivery kinetics and

their changes during degradation and erosion, in order to ensure an effective dose, without reaching toxic levels.

The ability to predict the evolution of biodegradable polymers over the course of degradation would enhance the biodegradable drug eluting implant design process. When conditions are simple and the desired life-time of the implant is fairly well-known, a “trial and error” approach has proven to be sufficient in producing reasonably reliable devices. On the other hand, in more complex situations when drug elution occurs in conjunction with mechanical loading, the lack of rational design tools has severely hampered the development of biodegradable implant technology.

Polymer degradation is the irreversible chain scission process that breaks polymer chains down to oligomers and finally monomers. Extensive degradation leads to erosion, which is the process of material loss from the polymer bulk. Such materials can be monomers, oligomers, parts of the polymer backbone, or even parts of the polymer bulk. Hence, degradation and erosion are distinct but related processes [12]. For polymeric matrices charged with drug, these phenomena should not be confused with *drug dissolution*, which is thought to describe the process of change of state from the initially solid drug into diffusible dissolved drug [13,14].

Drug release from stable polymers is usually governed by the mechanism of diffusion and is commonly referred to as diffusion-controlled drug release [15]. In the case of unstable polymers, whose matrices degrade and erode, drug release is affected by the physicochemical changes occurring. When the reactivity of the polymeric bond is low, resulting in greater timescales of reaction when compared to the timescale of diffusion, drug release occurs solely during the initial lifetime of the implant (as it diffuses) and may not be much affected by degradation and erosion. But on the other hand, if degradation occurs at a comparable timescale, drug release occurs in an erosion-controlled process [15]. A general improvement of the overall diffusive properties of the matrix enhances (and sometimes dictates) drug release, which essentially result from the dramatic morphological changes occurring due to degradation and erosion: e.g. degree of crystallinity initially increases due to preference of degradation of the amorphous phase, overall water sorption increases substantially, and macropores and voids form (cf. [16,17]).

The prevailing mechanism of biological degradation of synthetic aliphatic polyesters (the main class of biodegradable polymers used in biomedical applications, such as polylactic acid or polyglycolic acid) is random scission of the hydrolytically unstable backbone chain by passive hydrolysis [18]. The rate of swelling of common aliphatic polyesters is usually much higher than the rate of hydrolysis, hence the reaction occurs extensively through the swollen polymer bulk and the common mode of erosion observed in this class of polymers is bulk erosion [19,20].

Hydrolysis is a very intricate process that occurs at the molecular level [21]: Although the reactivity of each bond might be equal when considered individually, the large number of repeating units involved and their inherent steric environment, weak links, and branches may influence locally the rate of reaction. Ultimately, experiments

with gel permeation chromatography provide data to model the mechanism of degradation [22,23] and kinetic parameters are obtained from the evolution of experimentally obtained molecular weight distributions. An approach pioneered by Kuhn [24] and Montroll and Simha [25] employs combinatorial statistics to derive analytical solutions of the evolution of molecular weight distribution assuming that bond scission can be described with a known probability density function (e.g. equiprobable random scission, central Gaussian, or parabolic) and simple initial conditions. A second technique to model polymer degradation relies on a system of differential kinetic equations which describe the depolymerization rates of individual bonds and upon integration yield the temporal evolution of the molecular weight distribution [26], but a complete kinetic scheme represents thousands of differential equations even for modest size macromolecules. A third common method employs Monte Carlo simulations applied to populations of polymeric chains [27-29], a versatile approach that can technically overcome the simplifying assumptions needed on the others, but realistic simulations may require an excessive amount of computational resources.

Concerning polymer erosion, the choice of effective mathematical modeling tools is, however, not straightforward. Furthermore, existing erosion models are usually intrinsically linked to drug release models as most research efforts have aimed at both phenomena. Two main approaches to model erosion can be currently identified: models based on differential equations that consider the erodible material as a continuum where species dissolve and diffuse; and stochastic models that describe degradation and erosion as a probabilistic event (cf. [15] for a comprehensive review).

In the scope of the deterministic approach, Heller and Baker [30] pioneered with a simple model for degradation and drug release from bulk eroding polymers consisting of steady state water diffusion coupled with a reaction equation describing the kinetics of the degradation mechanism, and which in turn changed the permeability describing drug diffusion within the matrix. Lee [31] proposed a simplified model for surface erosion and drug release from polymer films based on the movements of two fronts, a diffusion front and an erosion front. Thombre, Joshi and Himmelstein [32-34] proposed a comprehensive theory for drug release, water penetration, and erosion from eroding polymer and corroborated the theoretical findings with experimental results. Similar methods based on diffusion equations that account degradation, erosion, and drug release in more complex systems have been developed since [35-37], but the usual drawbacks of this kind of models are still present: the difficulty arising from modeling preferential degradation of the amorphous phase compared with the crystalline phase, and the incorporation of changes in the microstructure caused by the erosion mechanism and are usually specified within phenomenological reasoning.

On the other hand, stochastic models complemented with Monte-Carlo simulations to simulate surface or bulk eroding polymers have been developed (cf. Zygourakis [38] and Gopeferich and co-workers [15,39]). Erosion is described as being a probabilistic event and the polymer matrix as a grid of pixels, to each different property can be assigned and hence a distinction between the crystalline and amorphous phase can be considered. By

removing eroded pixels from the grid, the stochastic evolution of a polymeric matrix was obtained and experimentally measurable parameters, such as porosity and weight loss, were calculated. Erosion fronts and a distinction between erosion modes were inferred from the results and their fit to experimental data allowed the determination of erosion rate constants. Although such models have shown good performances because of their versatility to account a multitude of phenomena occurring due to degradation (e.g. the formation of voids inside the polymer bulk as well as in the treatment of moving fronts for surface erosion), their coupling with deterministic models based on Fick's law for drug release is not straightforward. Furthermore, the computational cost associated with Monte-Carlo simulations is generally much larger than the one of standard (finite difference or finite element) methods for partial differential equations.

For these reasons, the aim of this work is to set up a general class of mathematical models capable to account for degradation (bond scission leading to physicochemical changes) and erosion (diffusion and washing away of byproducts leading to mass loss) and describe in a unified sense both bulk and surface modes. The model is developed within the deterministic framework of continuum mechanics and mixture theory. The key ingredients constituting the mathematical model are:

- (i) the description of the polymer as a polydisperse system which differentiates properties of chains of different sizes and the description of the matrix as a mixture of polymer, water and drug;
- (ii) polymer degradation kinetics, which allow the precise description of the evolution of population of chains of different sizes, accounting for their production and destruction due to hydrolytic scission;
- (iii) suitable constitutive laws to characterize transport properties of the mixture constituents through the polydisperse polymeric network, as well as their evolution as the nature of the network changes.

While the first item deals essentially with the nature of the system, items (ii) and (iii) describe the mechanisms of reaction and diffusion respectively. Phenomenologically, four distinct but related phenomena occur concurrently and must be described with the mathematical modeling:

- (i) *water uptake*: following in vivo implantation or in vitro submersion, water penetrates the initially dry and non-degraded polymeric network through the mechanism of diffusion;
- (ii) *hydrolytic scission*: as water becomes readily available in the vicinity of the chemical bonds, their likelihood of scission increases, leading to an overall molecular weight reduction;
- (iii) *polymer erosion*: smaller chains are progressively produced, which are more eager to dissolve and diffuse through the network leading to an overall mass loss;
- (iv) *drug release*: drug is released by the mechanism of diffusion through the polymeric matrix, whose material properties change due to degradation and erosion.

Because of the complexity of the phenomena at hand, the resulting set of equations can be rather cumbersome and several parameters are needed to characterize the behavior of the system. For this reason, a particular effort has been devoted to bring the equations to their non-dimensional form, putting into evidence a few characteristic quantities that completely determine the response of the polymeric matrix. Owing to this analysis, once the polymer properties are known, or more precisely, how diffusion and reaction occur, it is immediately understood whether the system will feature bulk eroding or surface eroding properties. Finally, numerical simulations based on the finite element method are employed to illustrate the behavior of the model for different polymer properties.

2 Mathematical Model

The design and construction of biodegradable drug delivery devices must involve a multitude of correlated physical phenomena: in most systems, water uptake, degradation, erosion and drug release depend on a complex, interrelated set of mechanisms including chemical reactions, multicomponent diffusion and physical changes in the system [33]. A mathematical model which incorporates all of the important mechanisms is a useful tool aiding the design of biodegradable drug release systems.

2.1 Polydisperse polymeric systems

Polymeric systems are usually polydisperse, i.e. they are constituted by a collection of molecules of different sizes instead of being composed solely by molecules of a single chain size (classical exceptions are most naturally synthesized proteins). This is a consequence of the random nature of polymerization reactions.

Scalar averages of the entire population of molecules constituting the polydisperse system, namely the number-average molecular weight and the weight-average molecular weight (M_n and M_w , respectively), are quantities highly appraised by experimentalists as they allow polymeric samples to be described by single scalar quantities (cf. [40,41]). The polydispersity index, defined as the ratio of M_w and M_n , tries to capture the broadness of the population. Nevertheless, the distribution of molecular weights has been shown to be important in many diverse applications, including flow of melts and solutions, aging and weathering behavior, adhesion, and flocculation [41]. When dealing with high molecular weights (usually with chains of lengths of tenths or hundredths of thousands), it becomes convenient to treat distributions as being continuous rather than discrete [22,23]. The most popular experimental technique for measuring distributions of molecular weight in a polymer system is known as gel permeation chromatography or size exclusion chromatography. The principle of the method consists on the time dependent filtration of a mixture of small and large molecules through a column packed with porous beads, where the filtration time of each molecule is distinguished according to its size [40,41].

In our modeling of a polydisperse polymeric system, the polymeric system is discretized into N number of constituents of different average degrees of polymerization (the number of repeating units in a chain, which is directly related to the molecular weight of a chain through the monomer molar mass M_0). The degree of polymerization, $x \in]0, \infty[$, is partitioned into N mutually exclusive equidistant partitions P_i of average degree of polymerization \bar{x}_i for $i=1, 2, \dots, N$. One has $\bar{x}_i = i \bar{x}_1$, for $i=1, \dots, N$ and

$$P_i = \left[\bar{x}_i - \frac{\bar{x}_1}{2}, \bar{x}_i + \frac{\bar{x}_1}{2} \right], \quad \text{for } i=1, \dots, N. \quad (1)$$

Average degree of polymerization \bar{x}_1 represents the average degree of polymerization of the smallest chains, i.e. “quasi-monomeric”. The average size of the chains increases as i increases and \bar{x}_N corresponds to the average degree of polymerization of the longest “quasi-polimeric” chains. In between, there is the entire range of $N-2$ “quasi-oligomeric” different average chain sizes.

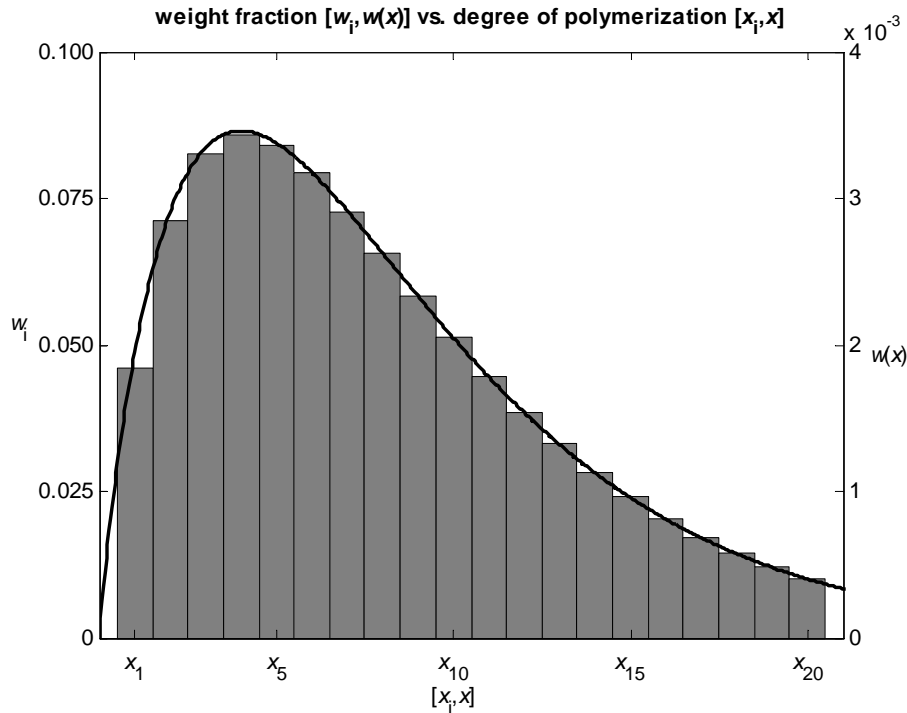


Figure 1. Weight fraction of constituents of a polydisperse polymeric system. A Schultz distribution is discretized into $N = 20$ partitions. The continuous distribution of weight fractions $w = w(x)$, a result commonly obtained experimentally, is well approximated with a finite number of partitions.

Let w_i for $i=1, 2, \dots, N$ be the weight fraction of chains inside partition P_i with average degree of polymerization \bar{x}_i . Weight fractions w_i are a finite discretization of the continuous weight fraction distribution $w = w(x)$ over the range of degree of polymerization $x \in]0, \infty[$ – e.g. a Schulz distribution (cf. [40,41]) given by

$$w(x) = \frac{1}{\Gamma(a+1)} \left(\frac{a}{x_n} \right)^{a+1} x^a \exp\left(-\frac{a}{x_n} x \right), \quad (2)$$

where x_n and x_w are the number-average and weight-average degrees of polymerization respectively, Γ is the Gamma function and constant a is a measure of the polydispersity of the system (as $x_w/x_n = 1 + 1/a$), is discretized through integration over the corresponding partition P_i , i.e.

$$w_i = \int_{P_i} w(x) dx, \quad (3)$$

for $i = 1, \dots, N$ (cf. Figure 1, obtained with $N = 20$ partitions ranging from $x = 0$ to $x = 5x_n$ with $a = 0.9$).

2.2 Hydrolytic Scission and Degradation Kinetics

Although the reactivity of each bond may be identical when considered individually, details of the microstructure, such as weak links or steric environment, may influence the local rate of the reaction. This effect is exacerbated in mechanochemical reactions, where the magnitude of applied stress changes along the polymer backbone, leading to position-dependent reaction rates.

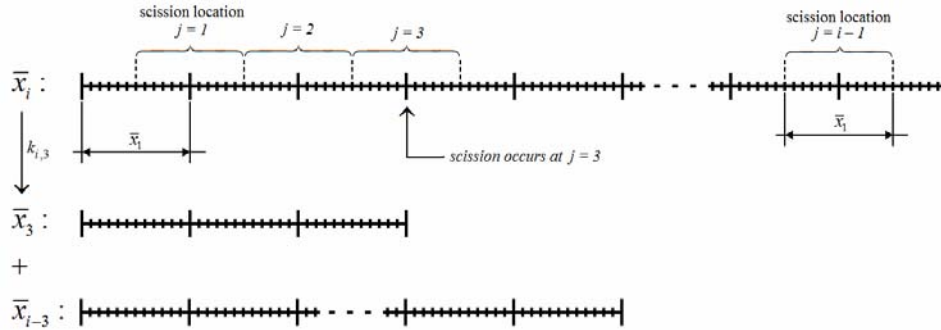
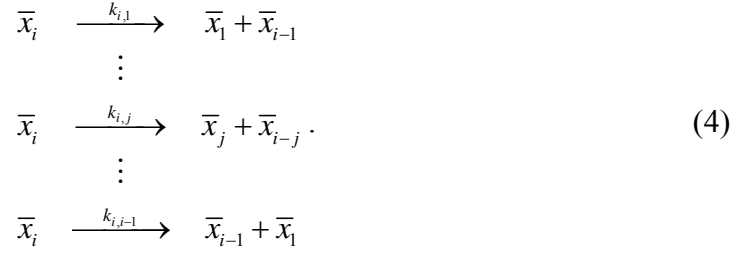


Figure 2. Hydrolytic scission kinetics. A chain of average degree of polymerization \bar{x}_i has $i-1$ scission locations, each of length \bar{x}_1 , which upon scission at location j yield chains of average degree of polymerization \bar{x}_j and \bar{x}_{i-j} , a reaction that occurs at rate $k_{i,j}$. In the example, scission occurs at $j=3$

The localization of the broken bond is a prerequisite of any molecular modeling of the degradation process. A chain of average degree of polymerization \bar{x}_i can be cleaved at $i-1$ different scission locations to yield chains of smaller average degree of polymerization, \bar{x}_j and \bar{x}_{i-j} , with $0 < j < i$ (cf. Figure 2, with $j=3$). Scission locations $j \in \{1, 2, \dots, i-1\}$ of chains of average degree of polymerization \bar{x}_i are composed of \bar{x}_1 individual polymeric bonds and to each corresponds one reaction rate $k_{i,j}$. A scission event occurring at any bond belonging to partition j results in a similar outcome: the production of chains of average degree of polymerization \bar{x}_j and \bar{x}_{i-j} . All possible outcomes of a chain of degree of polymerization \bar{x}_i are



The depolymerization kinetics can be described by means of a system of ordinary differential equations (cf. [22,23]). A polymeric chain of average degree of polymerization \bar{x}_i undergoes one of the reactions in (4). Let $n_i = n_i(t)$ denote the number of chains of average degree of polymerization \bar{x}_i existing at time t . In a closed system, the rate of change of number of chains n_i in partition P_i balances in the following way:

$$\left[\begin{array}{c} \text{rate of change} \\ \text{of chains } \bar{x}_i \end{array} \right] = - \left[\begin{array}{c} \text{rate of degradation} \\ \text{of } \bar{x}_i \text{ to smaller chains} \end{array} \right] + \left[\begin{array}{c} \text{rate of degradation} \\ \text{of chains } \bar{x}_k > \bar{x}_i \text{ to } \bar{x}_i \end{array} \right]. \quad (5)$$

The left hand side is given by a time derivative of n_i . The first term of the right hand side of equation (5) accounts for scission of chains of average degree of polymerization \bar{x}_i occurring at any of its scission locations $j=1,2,\dots,i-1$. The second term accounts that chains of average degree of polymerization \bar{x}_k with $k > i$ have two different locations, which upon scission, yield chains of average degree of polymerization \bar{x}_i : either when scission occurs at location i or at location $k-i$. Balance (5) becomes

$$\dot{n}_i = - \sum_{j=1}^{i-1} k_{i,j} n_i + \sum_{j=1}^{N-i} (k_{i+j,j} + k_{i+j,i}) n_{i+j}, \quad (6)$$

for $i=1,2,\dots,N$. Note that for $i=1$, the first sum is null (as the upper limit of the sum is smaller than the lower limit, a convention employed throughout this paper), which in fact means that chain of average degree of polymerization \bar{x}_1 do not undergo depolymerization.

The system of N ordinary differential equations (6) describes the degradation kinetics of chains of average degree of polymerization \bar{x}_i and governs the evolution of the population of polymer molecules in a closed system. Given an initial condition, kinetic equations (6) can be solved for any scission scheme with common numerical methods for 1st order ordinary differential equations. In the case of equally-probable random scission starting from a monodisperse initial condition, the kinetic equations have a closed form analytical solution. This problem was solved by Kuhn [24] and by Montroll and Simha [25] (cf. [26] and references therein for other cases with closed form analytical solutions).

2.3 Law of conservation of monomer

In a closed system, the total number of monomers existing in the degrading sample must remain the same. The total amount of monomers M in the polymeric mixture of N constituents of average degree of polymerization \bar{x}_i , for $i=1,\dots,N$ is given by

$$M(t) \equiv \sum_{i=1}^N n_i(t) \bar{x}_i . \quad (7)$$

The conservation law is mathematically stated as

$$\frac{\partial}{\partial t} M(t) = \sum_{i=1}^N \frac{\partial}{\partial t} n_i(t) \bar{x}_i = 0 . \quad (8)$$

Substituting equation (6) into equation (8) yields

$$\sum_{i=1}^N \sum_{j=1}^{i-1} k_{i,j} n_i \bar{x}_i = \sum_{i=1}^N \sum_{j=1}^{N-i} (k_{i+j,j} + k_{i+j,i}) n_{i+j} \bar{x}_i . \quad (9)$$

Noting that $\bar{x}_i = i \bar{x}_1$ for all $i = 1, \dots, N$, it is possible to assert the validity of equality of equation (9), i.e. the equations governing the dynamics of the population of molecules respect the law of conservation of monomers.

2.4 Fick's 1st law of diffusion

Constituents have the ability to diffuse along negative gradients [42]. This empirical law is coined as Fick's 1st law of diffusion, which relates the diffusive flux with the partial density gradient, i.e.

$$\mathbf{J} = -D \text{ grad } \rho , \quad (10)$$

where $\rho = \rho(\mathbf{x}, t)$ is the partial density of the constituent, $\mathbf{J} = \mathbf{J}(\mathbf{x}, t)$ is the diffusive flux of the constituent, \mathbf{x} is the position vector characterizing the control volume dV , and t is a scalar that represents time. Lastly, the diffusivity of the constituent, D , is the empirically derived material property that governs the diffusion of the constituent through the medium. Gradient operator appearing in equation (10) is the common spatial gradient, i.e. if $a = a(\mathbf{x})$ is a scalar field, then $\text{grad } \varphi = \partial \varphi / \partial \mathbf{x}$.

In our mathematical model, water and the polydisperse polymer system co-exist as constituents of the mixture. Fick's 1st law of diffusion for the water is given by

$$\mathbf{J}_w = -D_w \text{ grad } \rho_w , \quad (11)$$

where $\rho_w = \rho_w(\mathbf{x}, t)$, $\mathbf{J}_w = \mathbf{J}_w(\mathbf{x}, t)$, and D_w are the partial densities, the fluxes and the diffusivities of water respectively. For the polydisperse polymeric system, chains of each partition P_i follow a corresponding governing law,

$$\mathbf{J}_i = -D_i \text{ grad } \rho_i, \quad \text{for } i = 1, \dots, N , \quad (12)$$

where $\rho_i = \rho_i(\mathbf{x}, t)$, $\mathbf{J}_i = \mathbf{J}_i(\mathbf{x}, t)$, and D_i are, respectively, the partial densities, the fluxes, and the diffusivities corresponding to polymer chains of average degree of polymerization \bar{x}_i .

2.5 Fick's 2nd law of diffusion

Balancing of mass of constituents in an open control volume dV yields the reaction-diffusion equations that govern the physical problem. For the entire mixture,

mass balance states that total mass cannot be neither created nor destroyed. Note that in the case of a system with reaction equations, mass can not only diffuse through the boundary of dV but also can be inter-converted from one constituent to another. The balance of mass of each constituent in control volume dV reads as

$$\left[\begin{array}{c} \text{time rate of change of} \\ \text{mass of constituent in } dV \end{array} \right] = \left[\begin{array}{c} \text{net flow of mass of} \\ \text{constituent into } dV \end{array} \right] + \left[\begin{array}{c} \text{time rate of change of} \\ \text{mass of constituent due} \\ \text{to reactions in } dV \end{array} \right], \quad (13)$$

and limiting $dV \rightarrow 0$ yields a reaction-diffusion partial differential equation for the constituent

$$\dot{\rho} = \text{div}(D \text{ grad } \rho) + f, \quad (14)$$

where ρ is the partial density of the constituent, D is the diffusivity of the constituent, and f is the reaction rate of production or destruction of the constituent due to chemical reactions. Divergence operator div used in equation (14) is used in its common sense, i.e. if $\mathbf{v} = \mathbf{v}(\mathbf{x})$ is a vector field, then $\text{grad } \mathbf{v} = \partial \mathbf{v} / \partial \mathbf{x}$ and $\text{div } \mathbf{v} = \text{tr}(\text{grad } \mathbf{v})$.

Balancing of mass of each individual constituent yields the system of reaction-diffusion equations that constitute the mathematical model. For water, hydrolysis is accounted as a sink of water, i.e.

$$\dot{\rho}_w = \text{div}(D_w \text{ grad } \rho_w) - f_w, \quad (15)$$

where $f_w > 0$ is a reaction term accounting for the usage of water in the degradation reaction.

For each polymeric constituent, reaction terms accounting for the production and destruction of chains of average degree of polymerization \bar{x}_i are obtained from the kinetic equations (6), which were considered without any reference to space and where $n_i = n_i(t)$ described the number of chains of average degree of polymerization \bar{x}_i in the entire system. In order obtain the reaction-diffusion equations for polymeric constituents in terms of their partial densities, we consider $n_i = n_i(\mathbf{x}, t)$ as the scalar field that quantifies the number of chains of average degree of polymerization \bar{x}_i a in representative volume dV that corresponds to point \mathbf{x} at time t .

As $dV \rightarrow 0$, the relationship between partial density ρ_i and number of molecules n_i is $\rho_i(\mathbf{x}, t) = n_i(\mathbf{x}, t) \bar{x}_i M_0 / dV$, for $i = 1, \dots, N$, and where M_0 is the molecular mass of one monomeric unit. With this relationship, kinetic equations governing the populations can be obtained with respect to their partial densities, i.e. equation (6) becomes

$$\dot{\rho}_i(\mathbf{x}, t) = - \sum_{j=1}^{i-1} k_{i,j} \rho_i(\mathbf{x}, t) + \sum_{j=1}^{N-i} (k_{i+j,j} + k_{i+j,i}) \frac{\bar{x}_i}{\bar{x}_{i+j}} \rho_{i+j}(\mathbf{x}, t). \quad (16)$$

This equation is only valid if dV is a closed system. Scaling factors appearing in the second term of the right hand side are responsible for accounting the progressive increase of partial density as the corresponding molecule becomes large and can be perceived as part of the reaction rate if the reaction variable is the partial density.

When polymeric chains are able to diffuse in and out of dV through its boundary, the system of N reaction-diffusion equations for the polymeric constituents is given by

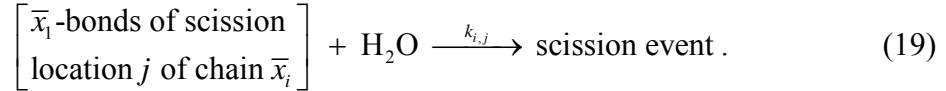
$$\dot{\rho}_i = \text{div}(D_i \text{grad } \rho_i) + \sum_{j=1}^N A_{ij} \rho_j, \quad (17)$$

where A_{ij} are given by the corresponding weighted sums of several relevant $k_{i,j}$ (cf. Eq. (16)) given by

$$A_{ij} = \begin{cases} 0 & \text{if } j < i \\ -\sum_{m=1}^{i-1} k_{i,m} & \text{if } j = i \\ (k_{j,i} + k_{j,j-i}) \frac{\bar{x}_i}{\bar{x}_j} & \text{if } j > i \end{cases} \quad (18)$$

2.6 Water consumption

One molecule of water is consumed with each scission reaction. A schematic reaction accounting for water consumption is



If $k_{i,j}$ is the rate of reaction of a scission location with \bar{x}_1 bonds at any of its bonds, then $k_{i,j}/\bar{x}_1$ is the rate of consumption of water in the scission event. The rate of change of the number of water molecules $n_w = n_w(\mathbf{x}, t)$ in a representative volume dV is given by

$$\dot{n}_w = -\sum_{i=1}^N \sum_{j=1}^{i-1} \frac{k_{i,j}}{\bar{x}_1} n_i, \quad (20)$$

which, with the relationship between n_w and ρ_w as $dV \rightarrow 0$, $\rho_w = n_w M_w / dV$ (where M_w is the molecular mass of water), yields the water consumption due to the chemical reaction

$$f_w = \sum_{i=1}^N \sum_{j=1}^{i-1} k_{i,j} \frac{M_w}{M_0 \bar{x}_1} \frac{\rho_i}{\bar{x}_i}. \quad (21)$$

When $i=1$, the inner sum is null as chains of average degree of polymerization \bar{x}_1 do not undergo scission.

2.7 Drug release

In addition to polymer degradation and erosion, drug release is accounted as it is a relevant topic in many biomedical applications that involve degradable polymers in conjunction with local drug elution. For drug cast into a polymeric matrix, drug release is a consequence of drug dissolution, which is thought to describe the process of change of

state from the initially solid drug into diffusible dissolved drug [13]. A classical modeling approach to describe drug dissolution employs a system of reaction-diffusion equations coupled by the Noyes-Whitney formula [43] to quantify the dissolution rate. Such models are intrinsically capable of making a difference between bulk or surface dissolution behaviors accordingly to the ratio of water and drug diffusion and the dissolution kinetics (e.g. [13]).

However for the sake of simplicity, we consider a model that relies on the assumption that the aqueous solubility of the drug is very high, and hence drug dissolution occurs very fast (e.g. comparing with the degradation time scale). As a result, drug release is a diffusional process; Fick's 1st law of diffusion, the diffusive flux is given by

$$\mathbf{J}_d = -D_d \text{grad } \rho_d, \quad (22)$$

where $\rho_d = \rho_d(\mathbf{x}, t)$, $\mathbf{J}_d = \mathbf{J}_d(\mathbf{x}, t)$, and D_d are, respectively, the partial density, diffusive flux and diffusivity of the drug. Balancing of mass for the drug yields

$$\dot{\rho}_d = \text{div}(D_d \text{grad } \rho_d), \quad (23)$$

as drug is not directly involved in the chemical reaction. Equation (23) could be improved by more general models for the process of dissolution of drug agglomerates to individual diffusible molecules. This could be modeled with an extra constituent accounting for the former and a reaction term in Equation (23) for the production of the latter (cf. e.g. [13]).

3 Constitutive Theory

Equations (15), (17) and (23) represent the balances of mass of each $N+2$ coexisting constituents of the mixture. So far, equation (23) governing the diffusion of the drug is uncoupled from the others, while equations (15) and (17) are coupled due to the hydrolysis reaction. Constitutive relationships for the diffusivities of each constituent and for the reaction rates must be specified; once known, the mathematical model is closed and can be solved.

Proposed constitutive relationships are phenomenologically reasoned, should depend on the particular polymeric system in question, and their specific forms must be asserted from carefully designed experiments. Nevertheless, their generality is sufficient to obtain a general class of mathematical models that describe the problem.

Constitutive equations should not be explicitly dependent on space and time. In one hand, one must expect that the mechanisms of reaction and diffusion should be independent of position and time as they describe the natural process. But on the other hand, hydrolysis and diffusion depend implicitly on space and time as the nature of their processes is influenced by the current and local state of the mixture.

3.1 Diffusion

Diffusion depends on the nature of the constituent in question and on the local characteristics of the mixture on which is diffusing. The diffusivity of each constituent is generally dependent on the current state of the polymeric network. We propose the general functional forms for the diffusivities of the constituents of the mixture

$$\begin{aligned} D_w &= D_w(\rho_1, \dots, \rho_N), \\ D_d &= D_d(\rho_1, \dots, \rho_N), \\ D_i &= D_i(\rho_1, \dots, \rho_N), \quad \text{for } i = 1, \dots, N \end{aligned} \quad (24)$$

In such way, equations (23) and (15) become coupled with equations (17), which become nonlinear. Furthermore, it should be expected that as the average degree of polymerization of polymeric chains increases, their diffusivity should decrease, i.e. $D_1 > D_2 > \dots > D_N$.

3.2 Hydrolysis

One common tool to describe the localization of the scission event along large chains is a scission probability density function, which distinguishes the likelihood of scission among scission locations in a chain of average degree of polymerization \bar{x}_i , i.e. the relationships among $k_{i,j}$ with i fixed and $j \in \{1, 2, \dots, i-1\}$. Some frequently encountered scission probability density functions are: random, parabolic, and central scission [22]. Random scission is defined with a constant probability density function along the length of the chain, e.g. $k_{i,1} = k_{i,2} = \dots = k_{i,i-1}$, for all $i = 2, \dots, N$, and is common amongst thermal reactions. Central scission is usually modeled with a Gaussian probability function and is more specific to stress-activated degradation, whereas parabolic scission results in a higher rate near the ends of the chain and is characteristic of the presence of long-chain branching. Nevertheless, any scission probability density function can be employed [22,23].

Hydrolysis happens due to the presence of water, hence depends on the partial density ρ_w . Therefore, the rate of scission at location j in a chain of average degree of polymerization \bar{x}_i , $k_{i,j}$, is a function of ρ_w . Moreover, in order to render sufficient generality to the mathematical model such that it accounts for generally nonlinear chemical reactions, the rate of hydrolysis depends on the existing amounts of polymeric constituents, i.e.

$$k_{i,j} = k_{i,j}(\rho_w, \rho_1, \dots, \rho_N), \quad \text{for } i = 2, \dots, N, j = 1, \dots, i-1. \quad (25)$$

Autocatalysis, a common nonlinearity occurring in hydrolytic reactions, can be described with general constitutive equation (25) in such a way that local presence of quasi-monomeric or small quasi-oligomeric chains enhances the rate of reaction.

4 I&BVP – Biodegradable Drug-Eluting Stent Coating

The partial differential equations that govern the reaction-diffusion system (Eqs. (23), (15), and (17)) with constitutive specifications for the reaction and diffusion processes (Eqs. (25) and (24) respectively), under certain conditions, possess general solutions. These solutions must be particularized with the specification of initial and boundary conditions. These are the conditions that particularize the equations into a description of a problem concerning one body with a particular geometry and subjected to defined conditions on its boundary.

The mathematical model is illustrated with a relevant initial and boundary value problem: cardiovascular stents coated with biodegradable polymers which are impregnated with drugs for local drug delivery are currently being employed [44-46]. Degradation, erosion and drug release profiles are of the utmost relevance for controllable clinical performance and of critical importance at the design stage.

4.1 Geometry

The polymeric coating is defined on a domain Ω of the three-dimensional Euclidean space such that $\mathbf{x} \in \Omega$ represents the position of a particle of the mixture that constitutes the stent coating. The boundary of the domain, $\partial\Omega$, is composed of two disjoint portions, i.e. $\partial\Omega = \partial\Omega_D \cup \partial\Omega_N$ and $\partial\Omega_D \cap \partial\Omega_N = \{\}$. $\partial\Omega_D$ is the boundary where a Dirichlet type boundary condition is applied, thought to describe the interaction of the coating with the surrounding medium (either fluid bath in an in vitro experiment, or the biological tissue in the in vivo situation). A Neumann boundary condition is specified in $\partial\Omega_N$ and describes the interaction between the polymeric coating and stainless steel stent bulk.

4.2 Initial Conditions

Initial conditions for the dependent variables at $t=0$ must be specified. The polymer network starts out dry, i.e. $\rho_w|_{t=0} = 0$, and with a homogeneous initial drug partial density, $\rho_d|_{t=0} = \rho_d^0$.

The initial state of the polydisperse polymeric system is homogeneous and is characterized by an initial degree of polymerization distribution $w^0 = w^0(x)$ and an initial total partial density $\tilde{\rho}^0$. The total partial density of polymer $\tilde{\rho} = \tilde{\rho}(\mathbf{x}, t)$ is a scalar that quantifies the amount of polymer existing at location \mathbf{x} at time t and is defined as

$$\tilde{\rho} \equiv \sum_{i=1}^N \rho_i. \quad (26)$$

From Eq. (3) and $w^0 = w^0(x)$, the initial weight fraction of chains of average degree of polymerization \bar{x}_i , w_i^0 , can be obtained for $i = 1, \dots, N$. Then, the initial conditions for the partial densities of polymer are $\rho_i|_{t=0} = w_i^0 \tilde{\rho}^0$.

4.3 Boundary Conditions

Boundary conditions must be provided at the boundaries of the polymeric coating. At $\mathbf{x} \in \partial\Omega_N$, the inner core of the stent prevents any diffusion of any constituents through this boundary into the stainless steel bulk. Impermeable boundary conditions for Eqs. (23), (15) and (17) are

$$\begin{aligned}\partial\rho_w/\partial\mathbf{x}|_{\mathbf{x}\in\partial\Omega_N} &= 0, & \text{for } t > 0, \\ \partial\rho_d/\partial\mathbf{x}|_{\mathbf{x}\in\partial\Omega_N} &= 0, & \text{for } t > 0, \\ \partial\rho_i/\partial\mathbf{x}|_{\mathbf{x}\in\partial\Omega_N} &= 0, & \text{for } t > 0, i = 1, \dots, N\end{aligned}\tag{27}$$

for water, drug, and polymeric constituents respectively.

At $\mathbf{x} \in \partial\Omega_D$, the coating contacts surrounding water or tissue. Water permeates through the interface accordingly to

$$\left[D_w \partial\rho_w/\partial\mathbf{x} + \pi_w (\rho_w - A\rho_w^\infty) \right]_{\mathbf{x}\in\partial\Omega_D} = 0, \quad \text{for } t > 0\tag{28}$$

where ρ_w^∞ is the concentration of water in the surrounding medium (either pure water or water content in tissue), π_w is the permeability of the interface to water molecules, and A is a partition coefficient (with $A \in [0,1]$) which describes the amount of water that the polymer-interface is able to uptake at saturation. Boundary condition (28) is responsible for allowing the mixture to achieve a homogeneous saturated state corresponding to $\rho_w = A\rho_w^\infty$ as $t \rightarrow \infty$. The ratio of π_w and D_w dictates the kinetics of water uptake.

Saturation and its kinetics should depend on the local characteristics of the mixture at the interface; therefore the permeability of water and the partition coefficient are specified as

$$\pi_w = \pi_w(\rho_1|_{\mathbf{x}\in\partial\Omega_D}, \dots, \rho_N|_{\mathbf{x}\in\partial\Omega_D}),\tag{29}$$

$$A = A(\rho_1|_{\mathbf{x}\in\partial\Omega_D}, \dots, \rho_N|_{\mathbf{x}\in\partial\Omega_D}),\tag{30}$$

i.e. functions of the partial densities of polymeric constituents. Note that as all partial densities of polymer tend to zero, $\rho_i \rightarrow 0$ for all $i = 1, \dots, N$, one should expect that $A \rightarrow 1$.

Drug at the boundary is dissolved and diffuses to the surrounding medium (or is absorbed by the tissue) but this phenomena is hampered by the appreciable size of drug molecules causing some entrapment in the mixture. Hence, a boundary condition of the type

$$\left[D_d \partial\rho_d/\partial\mathbf{x} + \pi_d \rho_d \right]_{\mathbf{x}\in\partial\Omega_D} = 0, \quad \text{for } t > 0\tag{31}$$

where π_d is the permeability of the interface to drug molecules, which is in turn generally given by

$$\pi_d = \pi_d(\rho_1|_{\mathbf{x}\in\partial\Omega_D}, \dots, \rho_N|_{\mathbf{x}\in\partial\Omega_D})\tag{32}$$

Boundary conditions for the N polymeric constituents at this interface must also be provided. As quasi-monomeric chains are small, the corresponding boundary condition should approach a perfect sink condition, i.e. when they reach the interface at $\mathbf{x} \in \partial\Omega_D$, they are readily dissolved in the surrounding water or absorbed by the tissue, i.e.

$$\rho_1|_{\mathbf{x} \in \partial\Omega_D} \approx 0, \quad \text{for } t > 0. \quad (33)$$

On the other side of the spectrum of degree of polymerization, as longest chains are unable to diffuse, an approximation to an impermeable boundary condition is expected, i.e.

$$\partial\rho_N/\partial\mathbf{x}|_{\mathbf{x} \in \partial\Omega_D} \approx 0, \quad \text{for } t > 0, \quad (34)$$

In between, a shift from both behaviors depicted by conditions (33) and (34) should exist. The general boundary condition,

$$[D_i \partial\rho_i/\partial\mathbf{x} + \pi_i \rho_i]|_{\mathbf{x} \in \partial\Omega_D} = 0, \quad \text{for } t > 0, \quad (35)$$

is specified for all $i = 1, \dots, N$ where D_i and π_i are the diffusivity and the permeability of polymeric chains of average degree of polymerization \bar{x}_i . The permeability describes the complex behavior occurring at the interface, either when the polymer is in contact with a fluid bath or in contact with biological tissue. The permeability of each constituent is generally specified to be a function of the current state of the network at the interface, i.e.

$$\pi_i = \pi_i(\rho_1|_{\mathbf{x} \in \partial\Omega_D}, \dots, \rho_N|_{\mathbf{x} \in \partial\Omega_D}). \quad (36)$$

Furthermore, it is expected that as the degree of polymerization of chains increase, their permeability at the interface should decrease, i.e. $\pi_1 > \pi_2 > \dots > \pi_N$.

5 Particular Constitutive Assumptions

In order to simplify the constitutive specification of the problem and illustrate the behavior of the mathematical model with numerical results, the system is particularized with several simplifications on the governing equations, in the constitutive specifications, and on the boundary conditions. Non-dimensionalization of the governing equations renders them applicable to any particular polymeric system and yields one non-dimensional number that relate the mechanisms of diffusion and reaction.

5.1 Diffusion

It is reasonable to consider scalar quantities that describe the characteristics of the polymeric network, e.g. the network partial density $\tilde{\rho}$ (cf. Eqs. (26)). In this way, instead of diffusivities of constituents depending on the entire set of polymeric partial densities, the specific forms of constitutive equations (24) are sole functions of the scalar measure of the state of the polymeric network. Constituents diffusivities are simplified to

$$\begin{aligned}
D_w &= D_w(\tilde{\rho}), \\
D_d &= D_d(\tilde{\rho}), \\
D_i &= D_i(\tilde{\rho}), \quad \text{for } i=1, \dots, N
\end{aligned} \tag{37}$$

In order to further simplify the constitutive specification, the diffusivity of water, D_w , is considered as the baseline diffusivity, i.e.

$$D_w = D \equiv D(\tilde{\rho}), \tag{38}$$

which we refer as D , the diffusivity in a network of polymeric partial density $\tilde{\rho}$. The diffusivity D_1 is smaller than the diffusivity of water as of chains of average degree of polymerization \bar{x}_1 are considerably larger than molecules of water. We will consider that their diffusivity is n times smaller than the baseline diffusivity of water, i.e. $D_1 = D/n$. Furthermore, the diffusivity of polymeric chains decreases as their size increases following the base n , i.e. the diffusivity of chains of average degree of polymerization \bar{x}_i is n times smaller than the diffusivity of chains of average degree of polymerization \bar{x}_{i-1} . Therefore, we specify

$$D_i = D_{i-1}/n = D/n^i, \quad \text{for } i=1, \dots, N. \tag{39}$$

Drugs commonly employed are usually large molecules. The diffusivity of the drug D_d is considered to be similar to the diffusivity of one of the polymeric constituents of comparable size. More precisely, there is one $k \in \{1, 2, \dots, N\}$ for which drug molecules and chains of average degree of polymerization \bar{x}_k are of comparable size and

$$D_d = D_k = D/n^k. \tag{40}$$

Equations (38)-(40) specify all the constituents diffusivities in terms of a single diffusivity, the baseline diffusivity $D = D(\tilde{\rho})$, which is the only material property characterizing the process of diffusion that needs to be specified: an exponential increase of diffusivity from $D = D^\infty$ towards $D = D^0$ as $\tilde{\rho} \rightarrow 0$ is assumed, i.e.

$$D(\tilde{\rho}) = D^\infty + (D^0 - D^\infty)e^{-\tilde{\rho}/\alpha}, \tag{41}$$

where α is a constant that reflect the variation of D with $\tilde{\rho}$.

Note that these assumptions – diffusion of polymer chains decreases with chain size (cf. Eq. (39)); the drug diffuses like a chain of comparable size (cf. Eq. (40)); and finally, the particular form for the dependence on the diffusing medium (cf. Eq. (41)) – are phenomenologically reasoned. They are employed in order to significantly decrease the complexity of the general constitutive assumptions and illustrate the behavior of the model.

5.2 Random Scission

Random scission is defined by all the polymeric bonds having the same scission probability, independently of to which chain they belong or where along that chain they are located. Each scission location is composed by a segment of \bar{x}_1 polymeric bonds, any of which upon scission causes the same effect. Therefore, for random scission, all

scission rates $k_{i,j}$ are equal for all chains of average degree of polymerization \bar{x}_i and corresponding $i-1$ scission locations, i.e.

$$k_{i,j} = k\bar{x}_i, \quad \text{for } i = 2, \dots, N \text{ and } j = 1, \dots, i-1, \quad (42)$$

where k is the rate of hydrolysis of the particular type of polymeric bond.

Instead of considering the general nonlinear rates of scission described by Eq. (25), we assume that random hydrolysis is a 1st order reaction with water, i.e. the polymeric bond has reaction rate that follows a linear relationship with partial density of water such that

$$k = k(\rho_w) = \tilde{k}\rho_w, \quad (43)$$

where \tilde{k} is the water dependent reaction rate of the polymeric bond. In such way, bilinear terms (bilinear on ρ_w and one ρ_i) appear in the reaction terms of Eqs. (15) and (17).

5.3 Geometry and Boundary Conditions

As the usual thickness of stent coatings is very small when compared with stent dimensions, the geometry of the body can be thought of as an infinite slab. A semi-inverse method can be employed to reduce the governing equations of the problem to one spatial dimension, z , the coordinate across the thickness of the infinite slab. The domain of the problem, Ω , is $z \in \Omega = [0, L]$, where L is the coating thickness. Neumann boundary $\partial\Omega_N$ corresponds to $z=0$, whereas $z=L$ represents the interface between the polymeric coating and the surrounding media. The dependent variables ρ_w , ρ_d and ρ_i for $i=1, \dots, N$ are functions of position z and time t , i.e. $\rho_w = \rho_w(z, t)$, $\rho_d = \rho_d(z, t)$, and $\rho_i = \rho_i(z, t)$ for $i=1, \dots, N$.

Boundary conditions at $z=0$ follow directly from Eq. (27). Water saturation boundary condition at $z=L$ is dictated by the partition coefficient, A , and the water permeability, π_w . Both depend on the characteristics of the polymeric network at the interface through $\tilde{\rho}|_{z=L}$.

For the former, we account that water uptake increases as the polymer erodes, leading to an eventual total replacement of the swollen network with a mixture solely composed of pure water. In its non-degraded state, the saturation condition is determined by $A^\infty < 1$. As erosion of the polymer at the interface leads to a decrease in $\tilde{\rho}|_{z=L}$, we propose the linear relationship

$$A = A(\tilde{\rho}|_{z=L}) \equiv 1 - (1 - A^\infty) \frac{\tilde{\rho}|_{z=L}}{\tilde{\rho}^0}, \quad (44)$$

such that as $\tilde{\rho}|_{z=L} \rightarrow 0$, $A \rightarrow 1$, which at saturation equilibrium results in a mixture characterized by $\rho_w \rightarrow \rho_w^\infty$ and $\rho_i \rightarrow 0$ for all $i=1, \dots, N$.

For the latter, we propose the following functional form

$$\pi_w = \pi(\tilde{\rho}|_{z=L}) \equiv \pi^\infty + (\pi^0 - \pi^\infty) e^{-\tilde{\rho}|_{z=L}/\beta}, \quad (45)$$

where π^∞ and π^0 are lower and upper bounds for permeability π_w , and constant β describe its variation with $\tilde{\rho}|_{z=L}$.

Similarly to the specification of the diffusivity of the polymeric constituents (cf. Eqs. (38) and (39)), all the permeabilities of polymeric constituents π_i for $i=1, \dots, N$ decrease following a base m , i.e.

$$\pi_i = \pi_{i-1}/m = \pi/m^i, \quad \text{for } i=1, \dots, N, \quad (46)$$

where it is considered that all chains permeate accordingly to a fraction of the baseline π_w specified by Eq. (45). Permeation of smaller chains at the interface occurs much faster than larger chains, which become inapt to permeate due to their size and entanglements.

Similarly as for the specification of the diffusivity of the drug, D_d (cf. Eq.(40)), the permeability of the interface to drug molecules is comparable to chains of similar size, i.e. of average degree of polymerization \bar{x}_k , with $1 \leq k \leq N$. Therefore, the permeability π_d employed in the corresponding boundary condition is given by

$$\pi_d = \pi_k = \pi/m^k. \quad (47)$$

5.4 Non-dimensional problem

In order to non-dimensionalize the dependent variables of the problem, the water density on the surrounding medium, ρ_w^∞ , the initial drug concentration, ρ_d^0 , and the initial polymer density, $\tilde{\rho}^0$, are employed accordingly. The non-dimensional dependent variables are distinguished by a superposed bar and are given by

$$\bar{\rho}_w = \frac{\rho_w}{\rho_w^\infty}, \quad \bar{\rho}_d = \frac{\rho_d}{\rho_d^0}, \quad \bar{\rho}_i = \frac{\rho_i}{\tilde{\rho}^0}, \quad \text{for } i=1, \dots, N. \quad (48)$$

With a characteristic length scale, the coating thickness L , non-dimensional space and differential operators $\overline{\text{grad}}(\bullet)$ and $\overline{\text{div}}(\bullet)$ are given by

$$\bar{z} = \frac{z}{L}, \quad \overline{\text{grad}}(\bullet) = L \text{grad}(\bullet), \quad \overline{\text{div}}(\bullet) = L \text{div}(\bullet). \quad (49)$$

The rate of random scission of a polymeric bond (Eq. (42)) yields a characteristic time scale of reaction; hence non-dimensional time and non-dimensional time differentiation are

$$\bar{t} = \tilde{k} \rho_w^\infty t, \quad \frac{\partial(\bullet)}{\partial \bar{t}} = \frac{1}{\tilde{k} \rho_w^\infty} \frac{\partial(\bullet)}{\partial t}. \quad (50)$$

Constitutively specified diffusivity D (cf. Eq. (41)) will be non-dimensionalized with D^∞ , i.e.

$$\bar{D} = \bar{D}(\bar{\rho}) = \frac{D}{D^\infty} = 1 + (D^0/D^\infty - 1)e^{-\bar{\rho}/\bar{\alpha}}, \quad (51)$$

where non-dimensional constant $\bar{\alpha} = \alpha/\tilde{\rho}^0$. The non-dimensional form of the governing equations is (the bar notation was dropped for convenience, all quantities are non-dimensional)

$$\dot{\rho}_w = \Lambda \operatorname{div}(D \operatorname{grad} \rho_w) - K \sum_{i=1}^N \frac{(i-1)}{i} \rho_w \rho_i, \quad (52)$$

$$\dot{\rho}_d = \Lambda \operatorname{div}\left(\frac{D}{n^k} \operatorname{grad} \rho_d\right), \quad (53)$$

$$\dot{\rho}_i = \Lambda \operatorname{div}\left(\frac{D}{n^i} \operatorname{grad} \rho_i\right) + \rho_w \bar{x}_1 \left[-(i-1)\rho_i + 2 \sum_{j=i+1}^N \frac{i}{j} \rho_j \right], \quad (54)$$

where non-dimensional number K is a ratio between molar volumes of water, V_w , and chains of average degree of polymerization \bar{x}_1 in the dry state, V_0 , i.e.

$$K = \frac{V_w}{V_0} = \frac{M_w}{\rho_w^\infty} \bigg/ \frac{M_0 \bar{x}_1}{\tilde{\rho}^0}, \quad (55)$$

and non-dimensional number, Λ , the Thiele modulus, is defined by

$$\Lambda = \frac{D^\infty}{L^2 \tilde{k} \rho_w^\infty}. \quad (56)$$

The Thiele modulus characterizes the relative rate of diffusive transport over the rate of degradation [33] and can be seen as the ratio between timescales of reaction and diffusion, i.e. $\Lambda = \tau^{\text{reaction}}/\tau^{\text{diffusion}}$ where $\tau^{\text{reaction}} = 1/(\tilde{k} \rho_w^\infty)$ and $\tau^{\text{diffusion}} = L^2/D^\infty$. Thus, if Λ is much larger than unity, the transport of the constituents governs the overall behavior of the system. On the other hand, if Λ is smaller than unity, the reaction is prevalent with respect to diffusion.

Boundary conditions must also be brought to a non-dimensional form. At $\bar{z} \equiv z/L = 0$, Eq. (27) follows directly. The permeability at the interface $\bar{z} = 1$ (cf. Eq. (45)) is non-dimensionalized with π^∞ , i.e.

$$\bar{\pi} = \bar{\pi}(\bar{\rho}|_{\bar{z}=1}) = \frac{\pi}{\pi^\infty} = 1 + (\pi^0/\pi^\infty - 1)e^{-\bar{\rho}|_{\bar{z}=1}/\bar{\beta}}. \quad (57)$$

Non-dimensional constants is given by $\bar{\beta} = \beta/\tilde{\rho}^0$. A non-dimensional functional form for the partition coefficient A (cf. Eq. (44)) is employed, i.e.

$$A = A(\bar{\rho}|_{\bar{z}=1}) \equiv 1 - (1 - A^\infty) \bar{\rho}|_{\bar{z}=1}. \quad (58)$$

Boundary condition for the water constituent (cf. Eq. (28)) becomes (the bar notation was once again dropped for convenience, all quantities are non-dimensional)

$$\left[\Lambda D \frac{\partial \rho_w}{\partial z} + \Gamma \Lambda \pi(\rho_w - A) \right]_{z=1} = 0, \quad \text{for } t > 0, \quad (59)$$

where non-dimensional number Γ relates the baseline permeability and diffusivity at the interface and is given by

$$\Gamma = \frac{L\pi^\infty}{D^\infty}. \quad (60)$$

Boundary conditions for the polymeric constituents (cf. Eq. (35)) become

$$\left[\Lambda \frac{D}{n^i} \frac{\partial \rho_i}{\partial z} + \Gamma \Lambda \frac{\pi}{m^i} \rho_i \right]_{z=1} = 0, \quad \text{for } t > 0. \quad (61)$$

Finally, boundary condition at $\bar{z} = 1$ for the drug follows from Eq. (31) and in its non-dimensional form is given by

$$\left[\Lambda \frac{D}{n^k} \frac{\partial \rho_d}{\partial z} + \Gamma \Lambda \frac{\pi}{m^k} \rho_d \right]_{z=1} = 0, \quad \text{for } t > 0, \quad (62)$$

which is similar to boundary condition imposed on chains of average degree of polymerization \bar{x}_k .

6 Methods

The numerical solution of the reaction diffusion system (cf. Eqs. (52)-(54)) was obtained with the implementation of a finite element formulation using COMSOL. A general algorithm to generate the formulation was constructed such that solutions with different N and Λ could be easily obtained.

The domain $\Omega = [0,1]$ was meshed with 100 quadratic Lagrange elements, a number that was sufficient to achieve mesh independency and describe in a suitable fashion sharp gradients associated with surface erosion. The maximum degree of polymerization considered was $\bar{x}_N = 600$, which for poly(L-lactic acid) is a commonly obtained degree of polymerization (e.g. [47]). Since the molar mass of the lactic acid monomer is $M_0 = 90$ g/mol, the molecular weight of the polymer sample is 54,000. The smallest average degree of polymerization \bar{x}_1 is obtained once the number of partitions $N = 20$ is defined, i.e. $\bar{x}_1 = \bar{x}_N / N = 30$. Molecules of such degree of polymerization feature a molecular weight of 2700 g/mol.

For simplicity, the initial polymer was considered to be monodisperse at the maximum average degree of polymerization. Nevertheless, any other initial condition could be employed with the specification of different initial weight fraction distributions. The considered initial conditions for the polymer are given by $\rho_1|_{t=0} = \dots = \rho_{N-1}|_{t=0} = 0$, $\rho_N|_{t=0} = 1$, and for the water and the drug by $\rho_w|_{t=0} = 0$ and $\rho_d|_{t=0} = 1$.

Although not necessary due to the non-dimensionalization procedure, the density of dry poly(L-lactic acid) is widely reported in the literature as $\tilde{\rho}^0 = 1.25$ g/cm³ [48,49], and typical drug content in stent coatings are reported to be in the range of 33%-67% of drug mass per polymeric mass, hence we set $\rho_d^0 = 0.5$ g/cm³ [50]. Drugs are typically average-sized molecules – e.g. Paclitaxel and Sirolimus (two drugs commonly employed in drug eluting stents) have a molecular weights of 853.906 g/mol and 914.172 g/mol [51,52]. Therefore, we set $k = 1$ (when $N = 20$ and $\bar{x}_1 = 30$), i.e. drug molecules behave similarly to chains of average degree of polymerization \bar{x}_1 .

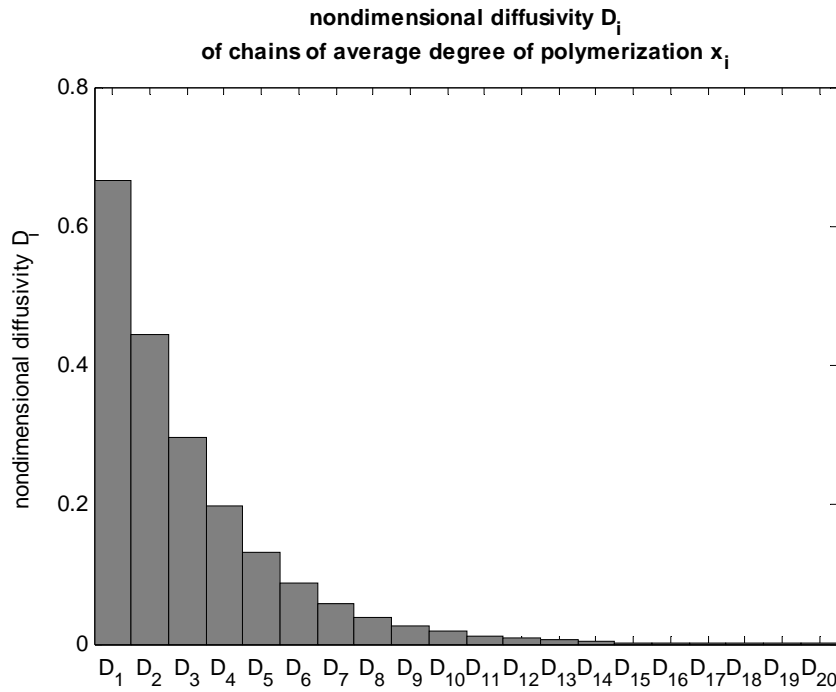


Figure 3. Relative diffusivity D_i of chains of different average degree of polymerization \bar{x}_i . As chains become smaller, their diffusivity increases. Diffusivity of water is considered to be the baseline, i.e. $D_w = 1$. A threshold behavior is employed, i.e. $D_i \approx 0$ for $11 \leq i \leq 20$, with the meaning that the largest chains barely diffuse through the network.

Changes in diffusivity and permeability occur due to degradation and erosion (described with constitutive relationships (41) and (45) respectively). We specify $D^0 = 1000D^\infty$, $\pi^0 = 1000\pi^\infty$, and $\bar{\alpha} = \bar{\beta} = 0.1$ with the meaning that diffusivity and permeability increase dramatically (one thousand-fold) as degradation and erosion lead to $\tilde{\rho} \rightarrow 0$. Constants $\bar{\alpha}$ and $\bar{\beta}$ are responsible for a strong nonlinear behavior with $D(\tilde{\rho} = 1) \approx D^\infty$, i.e. the initial condition.

Non-dimensional number Γ and bases n and m are chosen such that qualitative boundary conditions (cf. Eqs. (33) and (34)) are ensured. We consider that the shift between the approximations of the perfect sink condition for quasi-monomeric molecules towards the no-flux condition for the largest chains of average degree of polymerization \bar{x}_N occurs gradually, with both terms of the boundary condition (61) having the same relevance for species of medium degree of polymerization. Therefore, we set $\Gamma = (m/n)^{N/2}$ with $n = 1.5$ and $m = 3$. Although this choice of bases for the decrease of diffusivity is arbitrary and phenomenologically reasoned, it is expected that the decrease in diffusivity is nonlinear with increasing chain length and possess a threshold behavior, i.e. within a range of small chain sizes, diffusivity decreases somewhat but beyond some degree of polymerization, chains mostly become inapt to diffuse (Figure 3 shows the non-dimensional diffusivity D_i vs. \bar{x}_i with $N = 20$).

We employ data from Siparski et al. [53] for the partition factor of a non-degraded network of polylactic acid. The authors studied the degradability of polylactic acid films and found that at 50 °C and 90% relative humidity, the water uptake of the polymer was 0.7%, i.e. 0.007 g water/g PLA. Similar data under different testing conditions has been found by Cairncross et al. [54] and by Yoon et al. [55]. We set $A^\infty = 1\%$, i.e. the saturated non-degraded polymer uptakes water up to a partial density of $\rho_w = A^\infty \rho_w^\infty$. Note that due to degradation and erosion, $A \rightarrow 1$ as $\tilde{\rho} \rightarrow 0$ (cf. Eq.(58)).

Water consumption in the chemical reaction is directly related to non-dimensional number K (cf. Eq. (55), where for polylactic acid, $M_w = 18$ g/mol and $M_0 = 90$ g/mol). The non-dimensionalized form of the problem permits to disregard the need for particular values for the diffusion and reaction mechanisms, giving instead relevance to their ratio measured by the Thiele modulus. In order to be consistent, we employ data obtained for polylactic acid by Siparsky et al. [53]. They report reaction rates of the polymeric bond of $k = 5 \cdot 10^{-2} \text{ day}^{-1}$, and diffusivity of water inside the non-degraded initial network as $D^\infty = 10^{-7} \text{ cm}^2 \text{ s}^{-1}$. Considering a typical stent coating of $L = 10 \text{ }\mu\text{m}$ [56] and that the reaction occurs at saturated conditions of the initial network, one obtains $\Lambda = 1700$ (cf. Eq. (56)). Such Thiele modulus ($\Lambda \gg 1$) is indicative of bulk degradation and erosion, as the process of diffusion strongly dominates over the chemical reactions. We analyze Thiele modulus of $\Lambda = 0.01$ and $\Lambda = 1000$, which approximate the distinct ends of the spectrum of behaviors ranging in between pure surface and bulk erosion.

A useful scalar quantity to quantify degradation is the network average degree of polymerization, \tilde{x} , defined as

$$\tilde{x} \equiv \sum_{i=1}^N \rho_i \bar{x}_i, \quad (63)$$

which is a scalar measure of degradation. while for drug release we analyze the amount of drug released up to a certain time, which is obtained by integration over the coating, i.e.

$$\frac{m_d^0 - m_d}{m_d^0} \equiv \frac{\int_{\Omega} \rho_d^0 - \rho_d \, d\Omega}{\int_{\Omega} \rho_d^0 \, d\Omega}. \quad (64)$$

The non-dimensional time employed in the non-dimensionalization procedure was taken with respect to the reaction process (cf. Eq. (50)) and in order to make a suitable comparison between drug release rates with different Thiele modulus, it is necessary to employ a non-dimensional time with respect to the diffusion process, \underline{t} , which is simply given by $\underline{t} = \Lambda \bar{t}$.

We perform two types of analysis of the non-dimensional form of the governing equations:

(i) we look at the behavior of a closed system, where the polymer is assumed to be initially fully hydrated, $\rho_w|_{t=0} = A^\infty \rho_w^\infty$, and it does not interact with the exterior, i.e. with Neumann conditions (27) at $z = 0$ and $z = 1$;

(ii) we analyze the case of an initially dry open system which is immersed in water at $t = 0$.

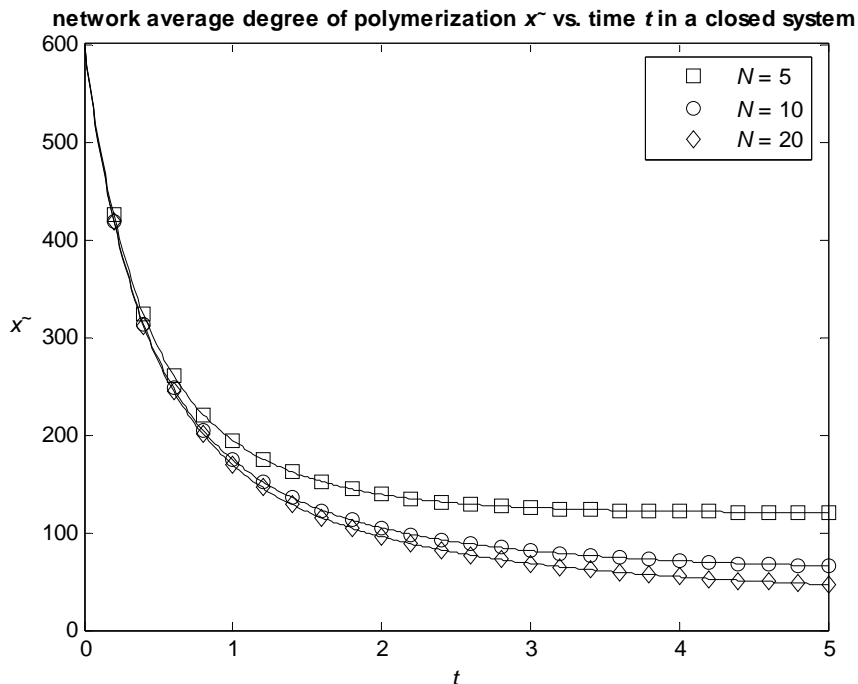


Figure 4. Decrease in network average degree of polymerization vs. time in a closed system. When both boundaries are adiabatic, degradation kinetics can be analyzed independently of diffusion. Hydrolytic scission leads to a decrease in average degree of polymerization of the entire polymeric system and its rate of decrease is independent of the number of the partitions and equations describing the system. The state of maximum degradation, when all chains are of average degree of polymerization \bar{x}_1 , is better approximated as N increases.

7 Results

When considering a saturated closed system, the kinetics of degradation can be analyzed independently of diffusion. Starting from homogeneous (in space) initial conditions, diffusion does not occur, polymer does not escape through the boundaries, and the solution remains homogeneous and independent of z for all time t . We observed that degradation kinetics is N -independent, i.e. within numerical accuracy, degradation is independent of the number of partitions N and equations describing the system. The network average degree of polymerization, \tilde{x} (cf. Eq. (63) and Figure 4), decreases over time and its decreasing trend is increasingly better approximated as N increases.. Although the approximation of the solution generally improves as N increases; the improvement obtained with $N > 20$ does not compensate for the computational cost associated with solving a system of $N > 20$ equations. The initial rate is very well approximated even with $N = 5$. On the other hand, as N is related to the size of smallest

chains, the state of maximum degradation (when all chains are of average degree of polymerization \bar{x}_1) is better approximated as N increases.

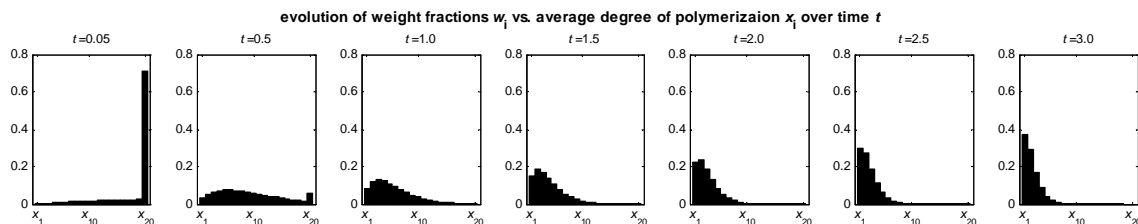


Figure 5. Temporal evolution of the weight fraction distribution w_i (of chains of average degree of polymerization \bar{x}_i). As scission takes place, larger chains yield smaller chains. As scission is random, a wide variety of chains sizes is produced initially (at time $t = 0.05$), but as time progresses, the number of smaller chains increase as a result of scission of larger chains. The distribution evolves from a monodisperse initial distribution given by $w_1 = \dots = w_{19} = 0$ and $w_{20} = 1$ towards another monodisperse distribution given by $w_1 = 1$ and $w_2 = \dots = w_{20} = 0$ at the state of maximum degradation.

Polymer degradation, which is perceived as the general reduction in chain size, is observed with the evolution of the distribution of weight fraction of the polymeric constituents (Figure 5, for $N = 20$, for non-dimensional time $t = 0.05, 0.5, 1.0, 1.5, 2.0, 2.5$, and 3.0). As time proceeds and scission takes place, the initially monodisperse polymer composed solely of chains of average degree of polymerization \bar{x}_{20} yields initially a wide variety of chains of all sizes. Then, the longer chains disappear and originate a large numbers of smaller chains.

When the system is open, polymeric chains can leave the system through its boundary at $z = 1$ and the smaller chains produced by degradation are more prone to diffuse. Erosion, which is perceived as the general decrease in partial polymer densities, ensues.

Depending on the value of the Thiele modulus, Λ , different modes of degradation and erosion occur. When $\Lambda = 1000$ (cf. Figure 6a and 6b), diffusion occurs at a much faster rate than the chemical reaction and water saturates the polymer across the entire thickness before significant scission takes place (Figure 6a). Polymeric byproducts are produced almost homogeneously across the thickness of the coating and their consequent diffusion is responsible for giving bulk erosion characteristics to the behavior of the reaction-diffusion system. Polymeric density $\tilde{\rho}$ decreases in a homogeneous fashion across the coating as smaller chains diffuse away (cf. Figure 6b). As degradation and erosion takes place, more water is able to enter and saturate the coating: ρ_w increases as saturation at the interface increases upon degradation (cf. Figure 6a). Ultimately, degradation and erosion leads to $\tilde{\rho} \rightarrow 0$ and $\rho_w \rightarrow 1$ everywhere, with the meaning that the entire coating eroded and was replaced by surrounding water.

When $\Lambda = 0.01$, the surface erosion mode is observed. Hydrolytic scission occurs at a much faster rate than diffusion in the network and degradation and erosion occur extensively near the boundary $z = 1$. The former is due to the local presence of water,

whereas the latter occurs due to the increased diffusivity of resultant byproducts. Due to water consumption in the chemical reaction, water molecules do not penetrate further into the coating before full degradation had occurred upstream. A front that travels from $z = 1$ to $z = 0$ develops, separating initially virgin and dry polymer (characterized by $\tilde{\rho} = 1$, $\rho_w \leq A^\infty$, and a network with high resistance to diffusion) from a region where the fully degraded and eroded polymer gave place to the surrounding fluid (characterized by $\tilde{\rho} \rightarrow 0$, $\rho_w \rightarrow 1$, and very large diffusivities).

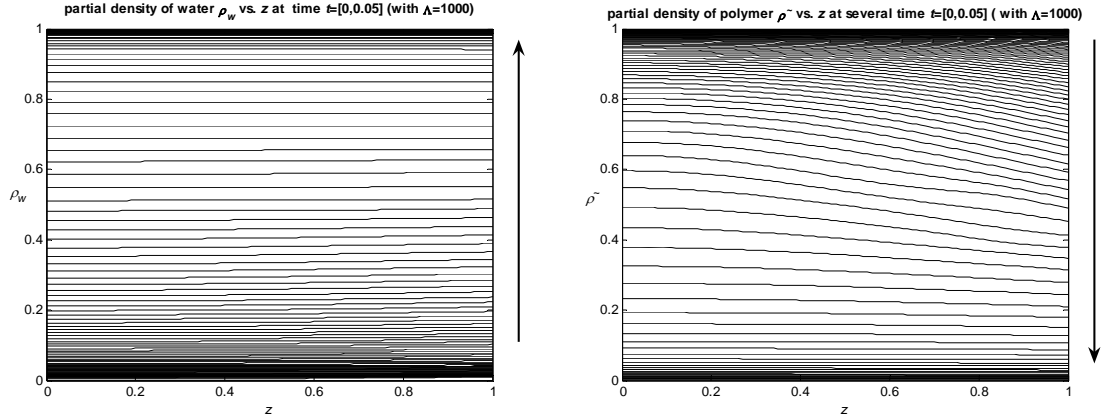


Figure 6. Profiles of partial density of water ρ_w and partial density of polymer $\tilde{\rho}$ at several t for $\Lambda = 1000$. Bulk erosion is clearly observed. The partial density of polymer decreases almost homogeneously from its initial value $\tilde{\rho} = 1$ towards $\tilde{\rho} \rightarrow 0$ and is progressively replaced by surrounding water as the eroded polymer is able to uptake more water, i.e. initial saturation promotes $\rho_w(t = 0) = A^\infty$ but $A^\infty \rightarrow 1$ and $\rho_w \rightarrow 1$ as the material erodes.

Drug release also shows dramatic changes when changing the Thiele modulus. As Λ decreases and the mode of erosion shifts from bulk degradation towards surface degradation, a change in drug delivery profile is observed. In bulk eroding matrices, drug release is dictated and controlled by diffusion, which is a first-order process, characterized by a straight line in a log-log plot of total amount of drug released vs. time (cf. Figure 8). On the other hand, when decreases in Λ promote a shift to surface erosion mode, the release of drugs departs from the 1st order release rate characterized by the sole diffusion mechanism and is enhanced due to degradation and erosion, i.e. drug release becomes erosion-controlled. This enhancement leads to drug release occurring faster in surface eroding polymers than in a bulk (higher slopes in Figure 8) and moreover, it evolves in a nonlinear way.

8 Discussion

Biodegradable polymers have been usually classified as either surface eroding or bulk eroding polymers and most models start from this assumption at inception [20]. Surface erosion has been modeled with moving boundaries (cf. e.g. [31]) and bulk

erosion with spatially independent degradation rates reflecting the steady state water saturation condition that usually occurs before appreciate scission takes place (cf. e.g. [30]). Furthermore, degradation and erosion are often blurred and modeled in a conjunct manner.

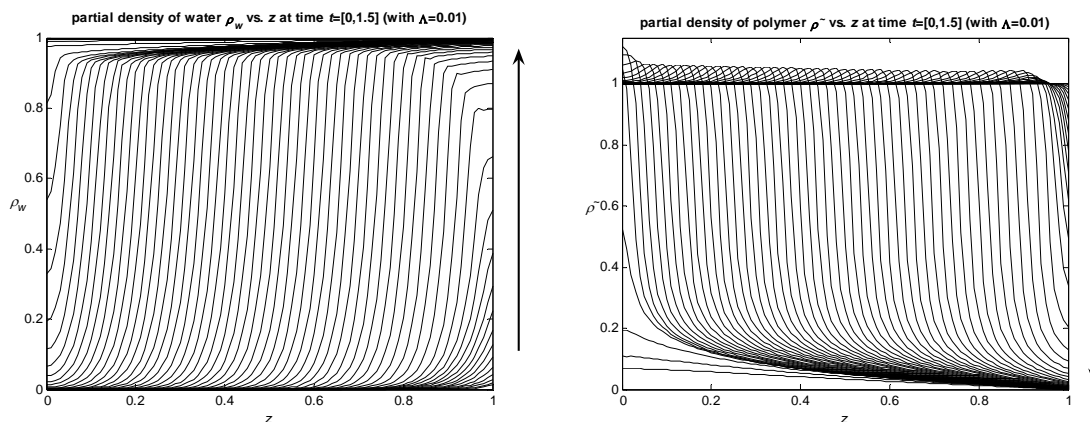


Figure 7. Profiles of partial density of water ρ_w and partial density of polymer $\tilde{\rho}$ at several t for $\Lambda = 0.01$. Surface erosion is clearly observed. A front develops and travels from $z = 1$ towards $z = 0$. The partial density of polymer decreases sharply at the surface and hardly any changes occur upstream. The front separates two regions: non-degraded and dry polymer existing upstream (characterized by $\tilde{\rho} = 1$) and pure surrounding water downstream ($\tilde{\rho} \rightarrow 0$ and $\rho_w \rightarrow 1$).

Taking this into consideration, the proposed model separates the distinct but related phenomena of polymer degradation, thought to be the chemical changes occurring in the material due to hydrolysis, and polymer erosion, the process of diffusion and washing away of degradation byproducts. Hydrolytic scission leads to a marked decrease in chain size as larger molecules are cleaved into smaller. Then, as smaller chains are eager to diffuse, erosion ensues [19]. Water uptake occurs immediately after as the matrix is inserted in a fluid bath or implanted in vivo and drug release follows during the expected release time [4].

Our model is deterministic in nature and is based on the theory of mixtures. We consider the polymeric system as a mixture of co-existing water, drug, and N different polymeric constituents, each comprising a range in chain size and characterized by a particular average degree of polymerization \bar{x}_i , for $i = 1, \dots, N$. Polymeric systems are polydisperse and scission is responsible for changes in the distribution of degree of polymerization as smaller chains originate at the expense of larger ones [22,23]. Without considering the temporal evolution of distribution of degree of polymerization, it is impossible to account for changes occurring due degradation in a precise and systematic mode.

Scission kinetics has been successfully modeled by means of a discrete approximation of the molecular weight distribution. This approach gives rise to discrete lumped models of a finite number of average degrees of polymerization [22,23]. We are able to assert the validity of the discrete kinetic model by proving that the resulting

discrete kinetic equations satisfy a monomer conservation principle, i.e. in a closed system, the total number of monomers is constant and independent of the extent of scission that had occurred (cf. Eq. (9)). Such conservation principle is independent of the discretization as the equality is valid considering any number of partitions N . Furthermore, scission promotes a marked decrease in network average degree of polymerization (cf. Figure 4) which is independent of N as well. Nevertheless, as the discretization of the degree of polymerization becomes finer, the state of maximum degradation is better characterized up to the perfect setting with $\bar{x}_1 = 1$. Overall, scission kinetics promotes the common shift to the left of the distribution of molecular weights (cf. Figure 5).

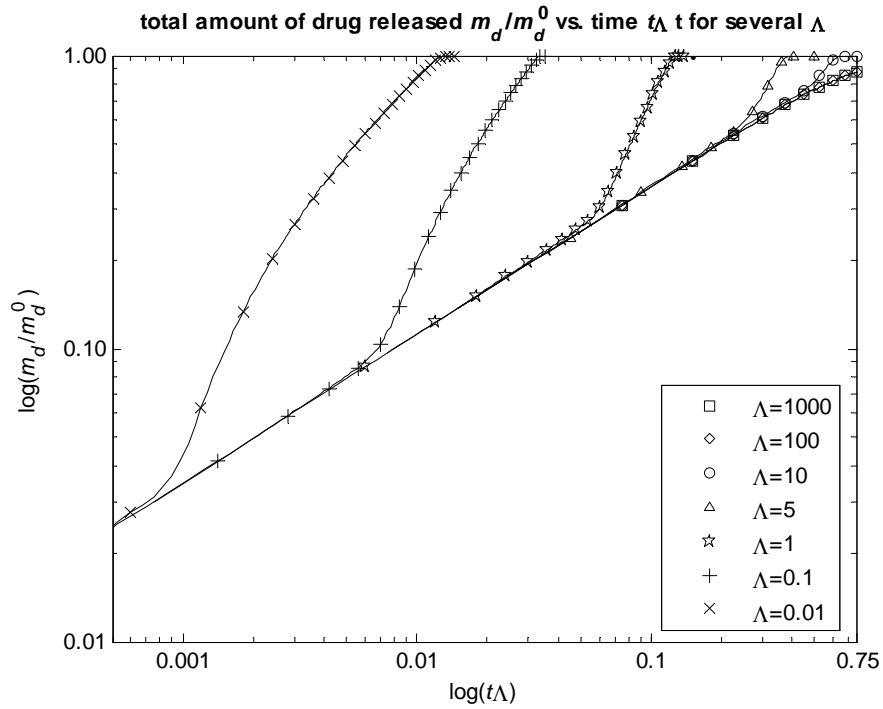


Figure 8. Log-log plot of total amount of drug released vs. time for several Λ . In bulk eroding systems, drug release is controlled solely by diffusion, a 1st order process that is characterized by a straight line in a log-log plot. As hydrolysis occurs at higher rates, the system shifts to a surface eroding mode and drug release becomes controlled by erosion – a departure from the straight line characterizing diffusion controlled drug release is observed. Furthermore, release rates in surface eroding polymers are nonlinear.

The governing equations that compose the mathematical model are based on of reaction diffusion equations, as these two mechanisms compete in polymer degradation and erosion. Chemical reactions occur spontaneously: existing reagents, water and polymeric bonds, have higher free energy than the resultant cleaved chain. Spatial density gradients of constituents are dissipated with the process of diffusion. The production of entropy associated with scission and the dissipative nature of diffusion are the driving forces that govern the behavior of the system. They are the only physical mechanisms that need constitutive specification. We consider they should not be dependent in space or

time explicitly; instead, they depend on the local nature of the mixture through its constituents frame-invariant partial densities, and hence depend implicitly on space and time.

We generally consider that diffusion of each constituent depends on the network in which it is diffusing (cf. Eq. (24)). Constitutive specification of the diffusivity of constituents could be further generalized with the inclusion of a dependence on the local partial density of water, ρ_w , i.e. the state of hydration of the mixture would enhance the diffusivity of constituents increasing their solubility and mobility. Similar arguments could be used to include or exclude a possible dependence of constituent diffusivities on the local amount of drug, as drug is also a part of the diffusing medium and can lead to a marked increase in porosity as is released – such considerations would result in a further nonlinear diffusion process (with respect to the corresponding dependent variables, ρ_w and ρ_d).

Hydrolysis must be specified as well. In order to allow for nonlinear chemical reactions, such as autocatalysis, we specify general forms for each reaction rate $k_{i,j}$ as functions of the partial densities of the polymeric constituents and water (cf. Eq. (4)). The relationship between rates $k_{i,j}$ for fixed i dictates the localization of scission along the length of each chain. Scission probability density functions are usually employed to describe such events and any scission probability density function can be employed [22,23]. The rates $k_{i,j}$ for fixed i are computed through integration of the scission probability density function over the length \bar{x}_i of the corresponding scission location.

We particularize the general constitutive model with several assumptions in order to obtain a tractable model whose behavior can be analyzed and illustrated. We consider the case of random scission, which is described by an equal likelihood of scission among all bonds and characterized by the rate of reaction of an individual polymeric bond. The rate of reaction was chosen to increase linearly with the amount of water yielding bilinear terms on the reagents. Autocatalysis was not accounted for, and if so, would result in a more complex specification of the rate of reaction of the individual polymeric bond. We consider that diffusion of each constituent is alike and has a simple decreasing behavior with a threshold as molecules increase in size (cf. Eqs. (38)-(40)). Furthermore, the dependence on the local nature of the network is considered to be a function of one scalar measure, the local density of polymeric constituents $\tilde{\rho}$. For simplicity, we assume that diffusivity increases one-thousand fold as the polymeric matrix erodes, i.e. as $\tilde{\rho} \rightarrow 0$.

Non-dimensionalization of the governing equations allows their applicability to any polymeric system and results in a set of non-dimensional parameters that characterize the behavior of the system. The Thiele modulus (cf. e.g. [33]), a ratio between the characteristic times of diffusion and reaction, is the only parameter responsible for promoting the dramatic changes in the response of the mathematical model that we associate to the commonly described bulk and surface modes for erosion.

The definition of the Thiele modulus (cf. Eq. (56)) depends on the intrinsic properties of the material: D^∞ , \tilde{k} , and the geometrical configuration of the device, which determines characteristic length scale L . As a result, the classification into surface of bulk

eroding polymers is not absolute, but depends on the device into consideration. By consequence, as is established previously [13,20], both behaviors can occur in the same polymeric system in devices of different characteristic lengths. With a similar argument, unstable polymers, which are known that are usually surface eroding, are characterized by higher reaction rates that lead to smaller Thiele numbers [32-34].

These observations further motivate the need for a unified model to account for both bulk and surface erosion. In this perspective, the efficacy of our model consists on the fact that remarkable different solutions of the system of governing equations are obtained with $\Lambda \gg 1$ and $\Lambda \ll 1$. This behavior results solely from the competing effects of reaction and diffusion working in conjunction with the nonlinear nature of the constitutive specification of the diffusivities, reaction rates and effective boundary condition for the interaction with the external medium.

In the case of bulk degradation and erosion (when Λ is large), slow chemical reactions result in slow changes in the mixture with which the diffusion mechanism can respond almost in a quasi-steady state mode. As chains become smaller, they diffuse away, which in turn allows increased water uptake due to an enhanced partition coefficient imposed at the boundary. All this spatial rearrangement of constituents happens at a fast pace when compared with the chemical reaction and therefore homogeneous rates of reactions and consequent bulk erosion are consequences of the differences in between reaction and diffusion time scales (cf. Figure 6).

On the other hand, in the case of very fast chemical reactions (when Λ is small), the nature of the equations become dramatically different and the response of the mathematical model can be associated with the commonly described surface mode of erosion. The initially dry polymer uptakes water near its surface and both are consumed in scission reactions. The smaller polymeric chains resulting from these reactions are able to diffuse much faster than the chains that originated them and consequently erosion of this superficial region happens. Due to erosion, the diffusivity over this region of the network and water uptake increases dramatically – in fact, changes in diffusivity that occurred due to degradation and erosion degenerate locally the governing equations (as D is considerably larger than all other coefficients). More precisely, as D is very large (cf. Fick's 2nd law of diffusion, Eq. (14)), the governing equations become of the form

$$\begin{aligned} \text{grad } \rho_w &\approx 0 \\ \text{grad } \rho_d &\approx 0 \\ \text{grad } \rho_i &\approx 0, \quad \text{for } i = 1, 2, \dots, N \end{aligned} \tag{65}$$

for all constituents. The strong nonlinear increase of diffusivities (cf. Eq. (41)) with boundary condition (28) is fundamental to confer the governing equations the ability to describe surface and bulk erosion. Indeed, as far as the diffusivities increase, the equations degenerate into the form of Eqs. (65). Simultaneously, water is allowed to penetrate freely into the eroded volume owing to the increasing partition coefficient A . As a result, this fully degraded and eroded region is characterized by constant density imposed by the boundary condition, i.e. pure water density ($\rho_w = 1$) and perfect sink

conditions ($\rho_d = \rho_1 = \dots = \rho_N = 0$) for all other constituents. A front develops and travels from the boundary inwards separating two distinct regions. Upstream remains only water as the polymer is fully degraded and eroded ($\rho_w \rightarrow 1$ and $\tilde{\rho} \rightarrow 0$) and downstream waits the initially dry and virgin polymer where water was not able to penetrate yet ($\tilde{\rho} = 1$ and $\rho_w = 0$).

Concerning drug release, the release kinetics (depicted in Figure 8) concur with former reported results (e.g. [33]) on the dynamics of controlled release from erodible polymers. The most important conclusion that can be derived is that drug release is strongly influenced by erosion mode of the delivery device. In particular, in agreement with the simulations and experimental data previously reported in the literature (e.g. [13] or [15] and references therein), we observe that drug release from surface eroding matrices is enhanced in comparison to drug release from bulk eroding matrices. Furthermore, this effect is evident even though, as in our case, the dominant force for drug release is solely diffusion rather than dissolution.

References

- [1] R. Langer, Drug delivery and targeting, *Nature* 392 (1998) 5-10.
- [2] J. Folkman, D.M. Long, The use of silicone rubber as a carrier for prolonged drug therapy, *J Surg Res* 4 (1964) 139-142.
- [3] G.W. Stone, S.G. Ellis, D.A. Cox, J. Hermiller, C. O'Shaughnessy, J.T. Mann, M. Turco, R. Caputo, P. Bergin, J. Greenberg, J.J. Popma, M.E. Russell, A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease, *New England Journal of Medicine* 350 (2004) 221-231.
- [4] A. Gopferich, Bioerodible implants with programmable drug release, *Journal of Controlled Release* 44 (1997) 271-281.
- [5] T. Hayashi, Biodegradable polymers for biomedical uses, *Progress in Polymer Science* 19 (1994) 663-702.
- [6] H. Laufman, T. Rubel, Synthetic absorbable sutures, *Surg Gynecol Obstet* 145 (1977) 597-608.
- [7] W.S. Pietrzak, D.R. Sarver, M.L. Verstynen, Bioabsorbable polymer science for the practicing surgeon, *Journal of Craniofacial Surgery* 8 (1997) 87-91.
- [8] S. Levenberg, R. Langer, Advances in tissue engineering, in: G.P. Schatten, (Ed), *Current topics in developmental biology*, vol. 61, Current topics in developmental biology 61, Elsevier Academic Press Inc, San Diego, 2004, pp. 113-134.
- [9] A. Colombo, E. Karvouni, Biodegradable stents: "Fulfilling the mission and stepping away", *Circulation* 102 (2000) 371-373.
- [10] T.L. Tammela, M. Talja, Biodegradable urethral stents, *BJU Int* 92 (2003) 843-850.
- [11] J.S. Soares, J.E. Moore, K.R. Rajagopal, Constitutive framework for biodegradable polymers with applications to biodegradable stents, *ASAIO Journal* 54 (2008) 295-301.
- [12] R.M. Ottenbrite, A.C. Albertsson, G. Scott, Discussion on degradation terminology, in: M. Vert, J. Feijen, A.C. Albertsson, G. Scott, E. Chiellini, (Eds), *Biodegradable polymers and plastics*, The Royal Society of Chemistry, Cambridge, 1992, pp. 73-92.

- [13] S.N. Rothstein, W.J. Federspiel, S.R. Little, A unified mathematical model for the prediction of controlled release from surface and bulk eroding polymer matrices, *Biomaterials* 30 (2009) 1657-1664.
- [14] P. Macheras, A. Iliadis, *Modeling in biopharmaceutics, pharmacokinetics, and pharmacodynamics*, Springer, New York, 2006.
- [15] J. Siepmann, A. Gopferich, *Mathematical modeling of bioerodible, polymeric drug delivery systems*, *Advanced Drug Delivery Reviews* 48 (2001) 229-247.
- [16] S. Li, H. Garreau, M. Vert, Structure-property relationships in the case of degradation of massive poly(α -hydroxy acids) in aqueous media - part 3: Influence of the morphology of poly(l-lactic acid), *Journal of Materials Science: Materials in Medicine* S (1990) 198-206.
- [17] S. Hurrell, R. Cameron, The effect of polymer morphology on the degradation and drug release from polyglycolide, *Biomaterials* 23 (2002) 2401-2409.
- [18] N.A. Weir, F.J. Buchanan, J.F. Orr, G.R. Dickson, Degradation of poly-l-lactide: Part 1: In vitro and in vivo physiological temperature degradation, *Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine* 218 (2004) 307-319.
- [19] A. Gopferich, Mechanisms of polymer degradation and elimination, in: A.J. Domb, J. Kost, D.M. Wiseman, (Eds), *Handbook of biodegradable polymers, Drug targeting and delivery*, Harwood Academic Publishers, Australia, 1997, pp. 451-471.
- [20] F.v. Burkersroda, L. Schedl, A. Gopferich, Why degradable polymers undergo surface erosion or bulk erosion, *Biomaterials* 23 (2002) 4221-4231.
- [21] M. Vert, S. Li, H. Garreau, J. Mauduit, M. Boustta, G. Schwach, R. Engel, J. Coudane, Complexity of the hydrolytic degradation of aliphatic polyesters, *Angewandte Makromolekulare Chemie* 247 (1997) 239-253.
- [22] T.Q. Nguyen, Kinetics of mechanochemical degradation by gel permeation chromatography, *Polymer Degradation and Stability* 46 (1994) 99-111.
- [23] T.Q. Nguyen, H.H. Kausch, Gpc data interpretation in mechanochemical polymer degradation, *International Journal of Polymer Analysis and Characterization* 4 (1998) 447-470.
- [24] W. Kuhn, The kinetics of the decomposition of high molecular chains, *Berichte Der Deutschen Chemischen Gesellschaft* 63 (1930) 1503-1509.
- [25] E.W. Montroll, R. Simha, Theory of depolymerization of long chain molecules, *Journal of Chemical Physics* 8 (1940) 721-727.
- [26] M. Ballauff, B.A. Wolf, Degradation of chain molecules .1. Exact solution of the kinetic-equations, *Macromolecules* 14 (1981) 654-658.
- [27] A.M. Kotliar, S. Podgor, Evaluation of molecular size distributions and molecular weight averages resulting from random crosslinking and chain-scission processes, *Journal of Polymer Science* 55 (1961) 423-436.
- [28] A.M. Emsley, R.J. Heywood, Computer modeling of the degradation of linear-polymers, *Polymer Degradation and Stability* 49 (1995) 145-149.
- [29] S.M. Bose, Y. Git, Mathematical modelling and computer simulation of linear polymer degradation: Simple scissions, *Macromolecular Theory and Simulations* 13 (2004) 453-473.
- [30] J. Heller, R.W. Baker, Theory and practice of controlled drug delivery from bioerodible polymers, in: R.W. Baker, (Ed), *Controlled release of bioactive materials*, Academic Press, New York, 1980, pp. 1-18.

- [31] P.I. Lee, Diffusional release of a solute from a polymeric matrix -- approximate analytical solutions, *Journal of Membrane Science* 7 (1980) 255-275.
- [32] A.G. Thombre, K.J. Himmelstein, A simultaneous transport-reaction model for controlled drug delivery from catalyzed bioerodible polymer matrices, *AIChE Journal* 31 (1985) 759-766.
- [33] A. Joshi, K.J. Himmelstein, Dynamics of controlled release from bioerodible matrices, *Journal of Controlled Release* 15 (1991) 95-104.
- [34] A.G. Thombre, Theoretical aspects of polymer biodegradation: Mathematical modeling of drug release and acid-catalyzed poly(ortho-ester) biodegradation, in: M. Vert, J. Feijen, A.C. Albertsson, G. Scott, E. Chiellini, (Eds), *Biodegradable polymers and plastics*, The Royal Society of Chemistry, Cambridge, 1992, pp. 214-225.
- [35] R.P. Batycky, J. Hanes, R. Langer, D.A. Edwards, A theoretical model of erosion and macromolecular drug release from biodegrading microspheres, *Journal of Pharmaceutical Sciences* 86 (1997) 1464-1477.
- [36] V. Lemaire, J. Belair, P. Hildgen, Structural modeling of drug release from biodegradable porous matrices based on a combined diffusion/erosion process, *International Journal of Pharmaceutics* 258 (2003) 95-107.
- [37] S. Prabhu, S. Hossainy, Modeling of degradation and drug release from a biodegradable stent coating, *Journal of Biomedical Materials Research Part A* 80A (2007) 732-741.
- [38] K. Zygourakis, Development and temporal evolution of erosion fronts in bioerodible controlled release devices, *Chemical Engineering Science* 45 (1990) 2359-2366.
- [39] A. Gopferich, R. Langer, Modeling polymer erosion, *Macromolecules* 26 (1993) 4105-4112.
- [40] P.J. Flory, *Principles of polymer chemistry*, Cornell University Press, Ithaca, 1953.
- [41] F. Rodriguez, C. Cohen, C. Ober, L.A. Archer, *Principles of polymer systems*, 5th edition, Taylor & Francis, New York, 2003.
- [42] J. Crank, *The mathematics of diffusion*, 2nd edition, Oxford University Press, New York, 1975.
- [43] A.A. Noyes, W.R. Whitney, The rate of solution of solid substances in their own solutions, *Journal of the American Chemical Society* 19 (1897) 930-934.
- [44] H. Storger, E. Grube, M. Hofmann, F. Schwarz, J. Haase, Clinical experiences using everolimus-eluting stents in patients with coronary artery disease, *J Interv Cardiol* 17 (2004) 387-390.
- [45] H. Honda, T. Meguro, K. Takizawa, S. Isoyama, Use of everolimus-eluting stent with a bioresorbable polymer coating for treatment of recurrent in-stent restenosis, *J Invasive Cardiol* 17 (2005) 112-115.
- [46] M.A. Beijik, J.J. Piek, Xience v everolimus-eluting coronary stent system: A novel second generation drug-eluting stent, *Expert Rev Med Devices* 4 (2007) 11-21.
- [47] G. Perego, G.D. Cella, C. Bastioli, Effect of molecular weight and crystallinity on poly(lactic acid) mechanical properties, *Journal of Applied Polymer Science* 59 (1996) 37-43.
- [48] J. Lunt, Large-scale production, properties and commercial applications of polylactic acid polymers, *Polymer Degradation and Stability* 59 (1998) 145-152.
- [49] D. Garlotta, A literature review of poly(lactic acid), *Journal of Polymers and the Environment* 9 (2001) 63-84.

- [50] C.D. Rogers, Drug-eluting stents: Clinical perspectives on drug and design differences, *Rev Cardiovasc Med* 6 Suppl 1 (2005) S3-12.
- [51] Paclitaxel, NIH Molecular Libraries - PubChem Compound Database CID: 36314.
- [52] Sirolimus, NIH Molecular Libraries - PubChem Compound Database CID: 6436030.
- [53] G.L. Siparsky, K.J. Voorhees, J.R. Dorgan, K. Schilling, Water transport in polylactic acid (pla), pla/polycaprolactone copolymers, and pla polyethylene glycol blends, *Journal of Environmental Polymer Degradation* 5 (1997) 125-136.
- [54] R.A. Cairncross, J.G. Becker, S. Ramaswamy, R. O'Connor, Moisture sorption, transport, and hydrolytic degradation in polylactide, *Applied Biochemistry and Biotechnology* 131 (2006) 774-785.
- [55] J.S. Yoon, H.W. Jung, M.N. Kim, E.S. Park, Diffusion coefficient and equilibrium solubility of water molecules in biodegradable polymers, *Journal of Applied Polymer Science* 77 (2000) 1716-1722.
- [56] M. Joner, G. Nakazawa, A.V. Finn, S.C. Quee, L. Coleman, E. Acampado, P.S. Wilson, K. Skorija, Q. Cheng, X. Xu, H.K. Gold, F.D. Kolodgie, R. Virmani, Endothelial cell recovery between comparator polymer-based drug-eluting stents, *Journal of the American College of Cardiology* 52 (2008) 333-342.

MOX Technical Reports, last issues

Dipartimento di Matematica “F. Brioschi”,
Politecnico di Milano, Via Bonardi 9 - 20133 Milano (Italy)

- 18/2009** J. SILVA SOARES, P. ZUNINO:
A mathematical model for water uptake, degradation, erosion, and drug release from degradable polydisperse polymeric networks
- 17/2009** M. LONGONI, C. MAGISTRONI, P. RUFFO, G. SCROFANI:
3D Inverse and Direct Structural Modeling Workflow
- 16/2009** G. ALETTI, C. MAY, P. SECCHI:
A functional equation whose unknown is $P([0; 1])$ valued
- 15/2009** S. PEROTTO, A. ERN, A. VENEZIANI:
Hierarchical local model reduction for elliptic problems I: a domain decomposition approach
- 14/2009** L. BEIRÃO DA VEIGA, M. VERANI:
A posteriori boundary control for FEM approximation of elliptic eigenvalue problems
- 13/2009** E. MIGLIO, A. VILLA:
A mathematical derivation of compaction and basin models
- 12/2009** S. BADIA, A. QUAINI, A. QUARTERONI:
Coupling Biot and Navier-Stokes equations for modelling fluid-poroelastic media interaction
- 11/2009** L. FORMAGGIA, A. VILLA:
Implicit tracking for multi-fluid simulations
- 10/2009** P. ZUNINO:
Numerical approximation of incompressible flows with net flux defective boundary conditions by means of penalty techniques
- 09/2009** E. AGOSTONI, S. SALSA, M. PEREGO, A. VENEZIANI:
Mathematical and Numerical Modeling of Focal Cerebral Ischemia